CONSEQUENCES OF CARDIOVASCULAR ADAPTATION TO SPACEFLIGHT: IMPLICATIONS FOR THE USE OF PHARMACOLOGICAL COUNTERMEASURES

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ABSTRACT

There is little evidence obtained from space flight to support the notion that occurrence of cardiac dysrhythmias, impaired cardiac and vascular function, and manifestation of asymptomatic cardiovascular disease represent serious risks during space flight. Therefore, the development of orthostatic hypotension and instability immediately after return from spaceflight probably reflect the most significant operational risks associated with the cardiovascular system of astronauts. Significant reductions in stroke volume and lower reserve for increasing peripheral vascular resistance contribute to ineffective maintenance of systemic arterial blood pressure during standing after spaceflight despite compensatory elevations in heart rate. The primary mechanism underlying reduced stroke volume appears to be a reduction in preload associated with less circulating blood volume while inadequate peripheral vasoconstriction may be caused partly by hyporeactivity of receptors that control arterial smooth muscle function. A focus for development of future countermeasures for hemodynamic responses to central hypovolemia includes the potential application of pharmacological agents that specifically target and restore blood volume (e.g., fludrocortisone, electrolyte-containing beverages) and reserve for vasoconstriction (e.g., midodrine, vasopressin). Based on systematic evaluations, acute physical exercise designed to elicit maximal effort or inspiratory resistance have shown promise as successful countermeasures that provide protection against development of orthostatic hypotension and intolerance without potential risks and side effects associated with specific pharmacological interventions.

Key words: blood volume; blood pressure; heart rate; stroke volume; cardiac output; peripheral vascular resistance

INTRODUCTION

The effects of extended exposure to microgravity environments on the cardiovascular system are well documented (Convertino, 2002). Although cardiovascular adaptations appear benign during a space mission, they have been manifested in reduced physiological or physical function upon return to Earth. As a result, a major focus of space-related research has been directed to the systematic development and evaluation of potential countermeasures. Among numerous treatments, specific pharmacological agents designed to enhance hemodynamic and autonomic functions have been considered or tested.

In 2000, the National Aeronautics and Space Administration (NASA) published their first draft of the Bioastronautics Critical Path Roadmap (BCPR) with the purpose of defining areas of biomedical research required for future long duration space flight. Specifically, the objective of the BCPR for human health and countermeasures was to focus on "understanding, characterizing, and counteracting the whole body's adaptation to microgravity, enabling healthy astronauts to accomplish mission objectives and return to normal life following a mission". The BCPR outlined specific critical risks of serious adverse health or performance consequences that would result from space flight. The priority for cardiovascular risks identified by the BCPR included 1) occurrence of serious cardiac dysrythmias; 2) diminished cardiac function; 3) manifestation of previously asymptomatic cardiovascular disease; 4) impaired cardiovascular response to orthostatic stress; and 5) impaired cardiovascular response to exercise stress. In 2004, a revised version of the BCPR reduced the identified priority for cardiovascular risks to include only the occurrence of serious cardiac dysrythmias and diminished cardiac and vascular function.

The purpose of this paper is to provide an assessment of proposed risk(s) to the cardiovascular system during space flight based on a critical review of data documented in the literature. An emphasis will be placed on the efficacy of specific pharmacological treatment of mechanisms associated with cardiovascular adaptations that lead to compromised operational performance of astronauts. An attempt will be made to provide perspectives on limitations and interpretations of these data in an effort to present future directions for development and/or implementation of effective pharmacological and non-pharmacological countermeasures for cardiovascular adaptation to space flight.

ASSESSMENT OF RISK TO THE CARDIOVASCULAR SYSTEM DURING SPACE FLIGHT

Occurrence of serious cardiac dysrhythmias. Despite numerous anecdotal reports, there is little evidence of a potential for occurrence of heart rhythm disturbances during space flight that may result in a serious cardiac event. For instance, no arrythmias were reported in a group of healthy astronauts during long-duration space missions despite a prolongation in QT interval (D'Aunno

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et al., 2003). No increase in cardiac dysrhythmias were reported from electrocardiogram (ECG) tracings collected on astronauts while performing their routine tasks and extravehicular activities (EVA) during short- (<14 d) or long-duration space missions (>14 d) (Fritsch-Yelle et al., 1996a; Rossum et al., 1997; Goldberger et al., 1994). Although a single isolated episode of a non-sustained, asymptomatic 14-beat ventricular tachycardia (VT) episode was reported in an astronaut during the second month of a mission on the Russian MIR space station (Fritsch-Yelle et al., 1998), further analysis raised the possibility that this VT episode might represent a normal variant if the ST elevation existing in the ECG tracing was also seen in the astronaut's previous resting tracing (Ellestad, 1998). Finally, "no pathology in the myocardial bioelectrical activity" was reported in 59 cosmonauts during MIR space missions of greater than 6-month duration (Golubchikova et al., 2003). Taken together, there is little evidence to suggest that the occurrence of serious cardiac dysrhythmias is a high risk to the health and well-being of astronauts during short- or long-duration space missions.

Manifestation of previously asymptomatic cardiovascular disease. The basis of the hypothesis that long-duration space flight may exacerbate previously undetected cardiovascular disease (e.g., coronary artery disease) is dependent upon the existence of evidence that supports one or both of two premises: 1) there have been cases within the astronaut community of undetected cardiovascular disease that existed before space flight; and/or 2) extended exposure to microgravity in some way aggravates pre-existing cardiovascular disease. Unfortunately, there are no published data to support the occurrence of either condition and, therefore, no evidence to suggest that conditions of space flight might cause a pre-existing cardiovascular disease to become symptomatic or accelerate the progression of the disease. Likewise, there is no published documentation to suggest that any astronauts have displayed the presence of asymptomatic cardiovascular disease prior to long duration missions. Therefore, in the currently selected astronaut population who undergo extensive medical screening prior to selection and mission in an effort to exclude the existence of clinical conditions, the risk of exacerbating a pre-existing asymptomatic cardiovascular disease appears to be very low.

Diminished cardiac function. It is clear from space flight experiments that stroke volume is significantly reduced upon return to earth (Buckey et al., 1996; Bungo et al., 1987; Convertino, 1990, 1995; Henry et al., 1977; Levine et al., 1996, 2002; Mulvaugh et al., 1991). Echocardiographic data demonstrated that the lower stroke volume was associated with reduced cardiac size (Bungo et al., 1987; Mulvaugh et al., 1991). Although a reduction in circulating plasma and blood volume that occurs with space flight is associated with less cardiac filling, data obtained from magnetic resonance imaging measurements obtained from 4 astronauts who participated in the 10-d D-2 NASA space mission revealed an average 14% reduction in left ventricular mass (Perhonen et al., 2001). These data were the first obtained from humans to offer evidence that there is a possibility for cardiac remodeling during space missions that might compromise myocardial function and contribute to lower stroke volume. In addition, there is evidence from ground simulation experiments that diminished cardiac compliance might reduce diastolic function and compromise cardiac filling (Levine et al., 1997). However, recent evidence generated from ground-based and flight experiments on animals suggests that smaller cardiac size simply may reflect the impact of negative caloric balance and reduction of body mass routinely observed in astronauts during space flight and results in a constant cardiac mass to body mass ratio (Ray et al., 2001). Regardless of any evidence for cardiac remodeling, measures of myocardial function curves before and after the 84-day U.S. Skylab mission (Henry et al., 1977), ejection fractions measured before and during the 237-day Russian Salyut-7 mission (Atkov et al., 1987), and arterial pulse wave velocities measured before and during the Russian 23-day Salyut-1 and 63-day Salyut-4 missions (Convertino, 1990) all suggest that there is little impact of long-duration exposure to microgravity on cardiac function. The space flight data probably reflect the effectiveness and importance of performing current intense exercise countermeasures in the maintenance of normal cardiac function. Therefore, the current evidence suggests that the risk of diminished cardiac function during or following space flight appears negligible in the presence of the current effective exercise space flight countermeasures.

Diminished vascular function. Hemodynamic responses during stand tests conducted on 14 astronauts following 9-14 days of space flight revealed that the distinguishing feature between astronauts who could (finishers) or could not (nonfinishers) complete 10 minutes of standing after these space missions was a significantly lower vasoconstrictor response in nonfinishers (Buckey et al., 1996). The relationship between low vasoconstrictive response and failure to complete stand tests has been corroborated in an additional 87 astronauts after space flight (Fritsch-Yelle et al., 1996b; Meck et al., 2004; Waters et al., 2002). These results obtained from astronauts following space missions have advanced the hypothesis that diminished vascular function may represent a significant cardiovascular risk of space flight. This hypothesis may be further supported by evidence of reduced vascular smooth muscle contraction with associated atrophic and morphological alterations generated from ground base animal models (Delp et al., 1993, 1999, 2000; Zhang et al., 1997; Zhang, 2001).

In contrast to attenuated vasoconstrictive responses reported in pre-syncopal astronauts, astronauts who display orthostatic stability after spaceflight exhibit elevated vascular resistance compared to preflight (Buckey et al., 1996; Fritsch-Yelle et al., 1996; Meck et al., 2004; Waters et al., 2002; Levine et al., 2002). These results have been corroborated in subjects exposed to

ground simulations of microgravity (Convertino et al., 1994; Kimaya et al., 2004). Therefore, there appears to be a discrepancy in vasoconstrictive response between non-presyncopal and presyncopal astronauts. A reduction in the vasoconstrictive reserve has been identified as a mechanism that contributes to orthostatic intolerance (Fu et al., 2004) and thus may provide an alternative explanation for a limitation in vascular function following adaptation to spaceflight. The vasoconstrictive reserve is defined as the difference between baseline and maximum vasoconstriction (Engelke et al., 1996). Both spaceflight and ground experiments have provided evidence that vasoconstriction during supine rest after exposure to microgravity is increased and associated with hypovolemia (Convertino, 1996, 1999; Convertino et al., 1994; Engelke et al., 1996; Gabrielsen et al., 1995). Increased peripheral vasoconstriction after return from space flight reflects a sympathetically-mediated reflex compensatory response to a reduction in stroke volume and cardiac output (Convertino et al., 2004a). A linear relationship between increased muscle sympathetic nerve activity and stroke volume was maintained between pre- and post-space flight tilt tests, suggesting a tight coupling (signaling) between stroke volume and sympathetic nerve activity (Levine et al., 2002). Since maximal vasoconstriction is finite, the elevated resting vasoconstriction associated with low circulating vascular volume and stroke volume represents a reduction in vasoconstrictive reserve and lowers the capacity to buffer orthostatic hypotension (Convertino, 1999; Engelke et al., 1996). It is therefore unclear based on the current evidence that any cardiovascular risk associated with space flight reflects a diminished vascular function or simply lower vasoconstrictive reserve secondary to hypovolemia.

Impaired cardiovascular autonomic functions. Adaptations of autonomically-mediated baroreflex mechanisms that control cardiac chronotropic responses and peripheral vascular resistance may contribute to inadequate blood pressure regulation after exposure to microgravity. Hypoadrenergic responsiveness has been hypothesized as a contributing mechanism to post-flight orthostatic intolerance as evidenced by a relationship between low blood norepinephrine and less vascular resistance in presyncopal astronauts (Fritsch-Yelle et al., 1996; Waters et al., 2002). Since sympathetic nerve activity, circulating norepinephrine and peripheral vascular resistance are all elevated in orthostatically-stable astronauts after space flight (Levine et al., 2002; Fritsch-Yelle et al., 1996; Waters et al., 2002), sympathetic withdrawal that occurs at the point of presyncope (Cooke & Convertino, 2003; Iwase et al., 2000) in addition to blood sampling in the supine posture of only the presyncopal astronauts (Fritsch-Yelle et al., 1996; Meck et al., 2004) may offer an explanation other than hypoadrenergic responsiveness for lower circulating norepinephrine reported in presyncopal astronauts.

Attenuation of cardiac vagal nerve traffic withdrawal induced by carotid baroreceptor stimulation was associated with presyncope during stand tests following exposure to simulated and actual microgravity (Convertino et al., 1990; Fritsch et al., 1992). Although heart rate increased with standing in syncopal subjects, their tachycardia was less than half that observed in the nonsyncopal subjects. These data provided the first evidence that attenuated carotid-cardiac baroreflex function may impair the capacity of tachycardic mechanisms to maximize elevations in heart rate, and subsequently cardiac output, during standing. Therefore, attenuation of baroreflex-mediated cardiac chronotropic responses induced by exposure to microgravity may represent a cardiovascular risk of limiting reflex compensatory tachycardic responses necessary to maintain adequate cardiac output.

Impaired cardiovascular response to orthostatic stress. Orthostatic hypotension and compromise following return from space flight has been well documented since the U.S. Gemini program (Hoffler, 1977) and presyncopal symptoms have been reported in 28% to 65% of mission specialists or scientists studied during stand or tilt test after returning from specific life science space missions (Buckey et al., 1996; Fritsch-Yelle et al., 1996; Meck et al., 2004; Waters et al., 2002). Impaired orthostatic performance in astronauts following their return from space flight has been associated with lower circulating blood volume, decreased stroke volume and cardiac output, and limited capacity to elevate peripheral vascular resistance (Buckey et al., 1996; Convertino, 1996; Fritsch-Yelle et al., 1996; Meck et al., 2004; Waters et al., 2002). It is clear that the inability of an astronaut to stand and perform an emergency egress from a spacecraft after landing could result in a life-threatening event. Thus, impaired cardiovascular response to standing after return from space may represent one of the highest risks to the safety, well-being, and performance of astronauts.

Impaired cardiovascular response to exercise stress. Numerous experiments using human subjects exposed to ground simulations of microgravity have demonstrated significant reduction in aerobic capacity (Convertino, 1995). More recently, a 22% reduction in aerobic capacity was demonstrated in 6 astronauts following only 9 or 14 days of space flight and was associated with reduced stroke volume (Levine et al., 1996). It is also clear that the reduced stroke volume during physical work in space is affected directly by lower cardiac filling, i.e., end-diastolic volume (Atkov et al., 1987). The relative reduction in maximal oxygen uptake following cardiovascular adaptation to ground simulations of microgravity is correlated highly with the relative magnitude of reduced circulating blood volume (Convertino, 1995), suggesting a close coupling between blood volume and cardiac filling. However, there is no evidence in the literature to suggest that a loss of 20% to 25% of aerobic capacity has impaired operational performance during or after space flight.

Summary of cardiovascular risks associated with space flight. There is little evidence obtained from space flight

to indicate that occurrence of cardiac dysrhythmias, impaired cardiac function, and manifestation of asymptomatic cardiovascular disease represent serious risks during space flight. Data from the literature provide the most convincing argument that impaired cardiovascular responses to orthostatic and exercise stresses represent the primary operational risks to astronaut health, safety and performance following space flight. Figure 1 illustrates the changes and interactions of mechanisms underlying the effect of cardiovascular adaptation to microgravity on orthostatic and exercise performance. It is clear from Figure 1 that the development of countermeasures should focus on restoring central blood volume, stroke volume and reserve for increasing peripheral vascular resistance.

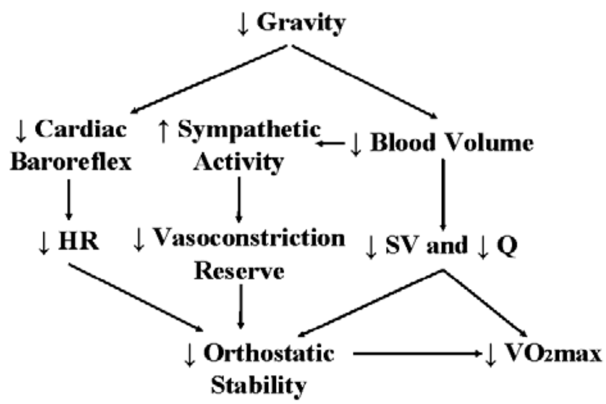

Figure 1. *Diagram outlining adaptations in underlying mechanisms of cardiovascular functions and their impact on operational functions in astronauts that result from exposure to microgravity (spaceflight).*

PHARMACOLOGICAL COUNTERMEASURES FOR CARDIOVASCULAR ADAPTATION TO SPACE FLIGHT

Extensive experiments conducted in both space flight and ground simulations provide a compelling argument that the most effective pharmacological countermeasures for protection of orthostatic and physical work performance should target plasma and/or blood expansion, autonomic dysfunction, and/or impaired vascular reactivity. Current clinical practices include the use of agents such as fludrocortisone or electrolyte containing beverages that expand circulating blood volume (Benditt et al., 1999; Raviele et al., 1996; Robertson & Davis, 1995); beta-adrenergic blockers such as propranolol, metoprolol, atenolol, nadolol, and esmolol in an effort to diminish the degree of cardiac mechanoreceptor activation or oppose peripheral vasodilatory effects of epinephrine (Benditt et al., 1999; Raviele et al., 1996); disopyramide in an effort to avoid vasovagal responses by counteracting parasympathetic activity (Benditt et al., 1999; Raviele et al., 1996); serotonin reuptake blockers such as fluoxetine hydrochloride and verlafaxine hydrochloride in an effort to reduce the effects of serotonin-mediated vasodepressor effects (Benditt et al., 1999); alpha-adrenergic agonists such as ephedrine, etilephrine or midodrine in an effort to increase venous tone and venous return as well as elevating peripheral vascular resistance by inducing arteriolar constriction (Benditt et al., 1999; Raviele et al., 1996; Robertson & Davis, 1995). Based on operational efficacy, the discussion of pharmacological agents used as potential countermeasures against deleterious effects of cardiovascular adaptation(s) to space flight will focus on specific experimentation and testing of blood volume expanders and vasoconstrictors.

Pharmacological expansion of circulating blood volume. Microgravity-induced hypovolemia contributes to orthostatic compromise after space flight. To counter this effect, U.S. astronauts currently adhere to a regimen of consuming a maximum of eight 1-g salt tablets with approximately 912 ml of fluid designed to make an isotonic saline drink approximately 2 h prior to reentry in an effort to restore blood volume (Bungo et al., 1985). Although a reduced orthostatic tachycardia following short duration space missions was encouraging during the initial use of saline loading (Bungo et al., 1985), exposure to microgravity for longer than 7 days failed to ameliorate orthostatic compromise in astronauts (Vernikos & Convertino, 1994; White et al., 1991). Despite the continued use of saline loading by astronauts in the U.S. space program, there is little evidence to suggest that taken alone it is effective against the development of post-flight orthostatic intolerance (Buckey et al., 1996).

The use of the mineralcorticoid fludrocortisone has been used clinically for nearly 40 years with some success to treat orthostatic hypotension, particularly in patients with an etiology linked to hypovolemia (Benditt et al., 1999; Robertson & Davis, 1995). Fludrocortisone acts to enhance sodium and fluid retention and has been reported to sensitize alpha-adrenergic receptors (Benditt et al., 1999). However, fludrocortisone appears to be most effective when consumed over days to weeks rather than on the day it is first administered (Robertson & Davis, 1995). Consequently, in a preliminary investigation, Vernikos and co-workers (1991) were the first to report that the administration of fludrocortisone with three doses over the final 24 hours of exposure to 7 days of simulated microgravity restored plasma volume in all subjects and protected orthostatic tolerance in 4 of 7 subjects who had previously become syncopal after head-down bed rest. In a subsequent investigation (Vernikos & Convertino, 1994), a more rigorously controlled experiment was conducted to compare the effectiveness of the current astronaut saline loading regimen to fludrocortisone as countermeasures for reduced plasma volume and orthostatic intolerance after spaceflight. Eleven healthy male subjects underwent a 3-day ambulatory baseline period followed by exposure to 7 days of 6° head-down bed rest. Treatments consisted of two volume expansion groups. One group (5 subjects) consumed 8 salt tablets (1 g NaCl per tablet) and 960 ml of water 2 hours prior to ambulation. The second group (6 subjects) consumed 0.2 mg oral dose of fludrocortisone at 0800 and 2000 h the day before and 0800 h the day the subjects got out of bed (2 hours before standing). After treatments, all subjects

attempted a 15-min unsupported stand test. Plasma volume decreased by 12% on day 7 of bed rest, and was restored by fludrocortisone but not by saline load (Fig. 2). Despite similar elevation in heart rate between the two groups, the group treated with saline loading experienced significant orthostatic hypotension compared to the fludrocortisone group (Fig. 3). Protection of arterial blood pressure during standing with fludrocortisone treatment was associated with restored vasoconstriction reserve and cardiac baroreflex function. Only 1 of 6 subjects showed syncopal symptoms in the fludrocortisone-treated group, whereas 4 of 5 subjects did so in the saline-load group. Acute fludrocortisone treatment appeared to have distinct advantages as a protective measure for orthostatic intolerance after exposure to ground simulation of microgravity.

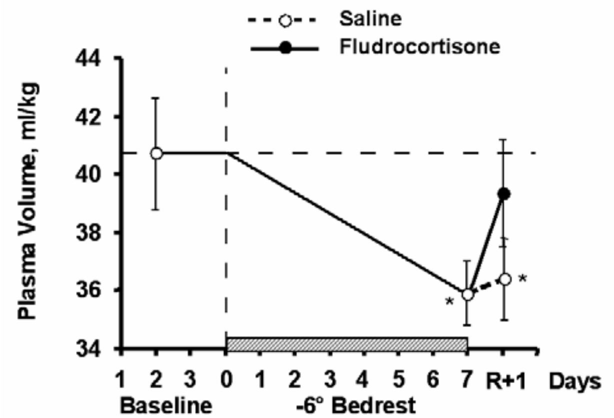

Figure 2. *Plasma volume before and at the end of head-down bed rest, and after treatment with saline (open circles and broken lines) and fludrocortisone (closed circle and solid line). Symbols represent mean (± SE). Asterisk indicates P < 0.05 compared to pre-bed rest baseline level. Data are modified from Vernikos and Convertino [1994].*

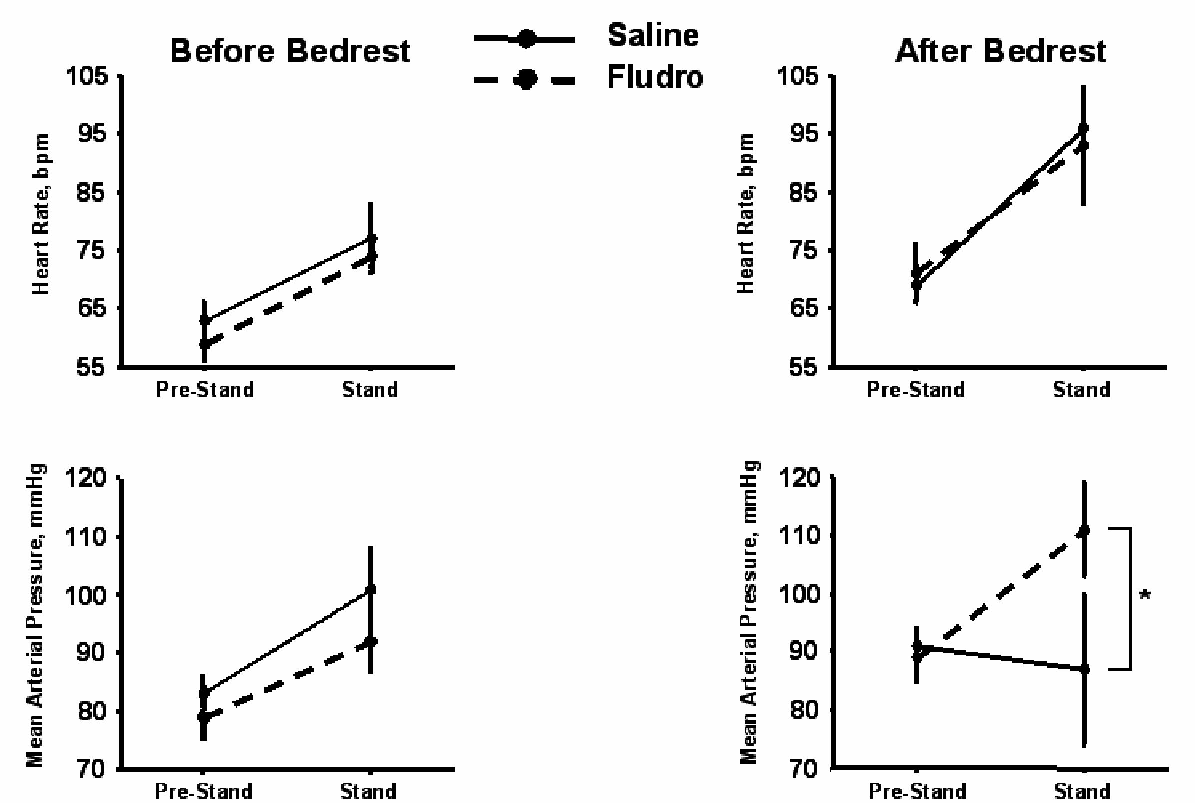

Figure 3. *Responses of heart rate (top panels) and mean arterial pressure (bottom panels) in subjects during supine baseline and at the end of 15 min of standing before (left panels) and after (right panels) bed rest after treatments with saline (closed circles and solid lines) and fludrocortisone (closed circles and broken lines). Symbols represent mean (± SE). Asterisk indicates P < 0.05 compared to saline treatment. Data are modified from Vernikos and Convertino [1994].*

Subsequently, the fludrocortisone countermeasure was tested on 7 male astronauts whose orthostatic responses were compared to 18 astronauts who received a placebo (Shi et al., 2004). Astronauts took either 0.3 mg fludrocortisone or placebo orally 7 hours prior to landing. Treatment with this single dose of fludrocortisone resulted in some protection of plasma volume but no protection of orthostatic tolerance. In the transition to spaceflight operational implementation, an effective dose of 0.2 mg taken 3 times during 24 hours prior to standing in the ground experiment was altered to a single dose of 0.3 mg taken 7 hours prior to landing in conjunction with the operational saline fluid loading countermeasure that was taken approximately 5 to 6 hours before landing. The difference in results of fludrocortisone application between ground and space may simply reflect significant alterations in the operational transition from the ground experiment to spaceflight testing. In the end, the use of

fludrocortisone as a countermeasure for post-spaceflight orthostatic intolerance was discontinued.

Use of adrenergic-receptor agents. The association of impaired peripheral vascular constriction with development of post-spaceflight orthostatic hypotension and syncope motivated consideration for the use of pharmacological agents that target the response of vascular adrenoreceptors. The administration of the non-specific β–adrenoreceptor antagonist propranolol has been proposed as a countermeasure targeted at increasing peripheral vascular resistance by inhibition of vasodilatory effects of circulating epinephrine on vascular smooth muscle (Sandler et al., 1985). However, this approach was abandoned when benefits of peripheral vasoconstriction were overridden by inhibitory chronotropic and inotropic effects that led to reduced orthostatic tolerance in ground experiments.

Most recently, the α_1-agonist drug midodrine was administered to 6 subjects one hour before a tilt stand test after they had completed exposure to 16 days of 5° head-down tilt (Ramsdell et al., 2001). Midodrine stimulates both arterial and venous constriction. Compared to the responses of 4 control subjects who received a placebo, midodrine significantly ameliorated development of hypotension and presyncope during the tilt test. Subsequently, this countermeasure was tested on a female astronaut who had become hypotensive and presyncopal during a stand test following her first 9-day space mission (Platts et al., 2004). After a second 11-day space flight, this astronaut received a single 10-mg dose of midodrine administered orally 1 hour prior to a tilt test. Her hemodynamic responses to the post-spaceflight orthostatic tests were compared. Compared to the supine posture, midodrine treatment was associated with stable systolic, diastolic and pulse pressures in contrast to dramatic reductions in these pressure in the absence of midodrine (Fig. 4). Stabilization of upright blood pressure with midodrine was associated with attenuated reductions in stroke volume and cardiac output (Fig. 5). Despite the effect of midodrine on arterial vasoconstriction, the elevation of peripheral vascular resistance during upright posture after space flight with midodrine treatment was similar to the preflight response and dramatically lower compared to the astronaut's post-spaceflight response following her initial mission when she experienced hypotension and presyncope (Fig. 5, lower right panel). Rather than arterial vasoconstriction, the lower peripheral vascular resistance in the presence of higher stroke volume suggests that the primary effect of midodrine after space flight in this astronaut was restoration of vasoconstrictive reserve by the improvement of central blood volume and cardiac filling (i.e., enhanced venoconstriction and venous return). These results may underscore the importance of central blood volume rather than autonomic dysfunction(s) as a primary mechanism of postflight orthostatic intolerance. The use of midodrine as a potential countermeasure for prevention of orthostatic intolerance following spaceflight awaits the results of continued successful implementation to future spaceflight missions.

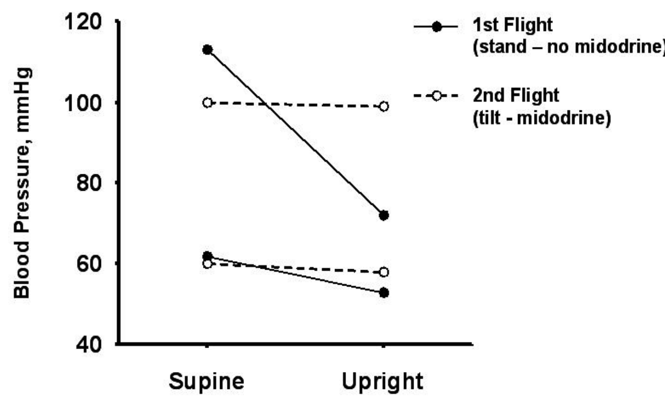

Figure 4. *Responses of systolic (top 2 lines) and diastolic (bottom 2 lines) arterial blood pressures in a female astronaut during a stand test following her first space mission (9 days) without midodrine (solid circles and solid lines) and during a tilt test following her second space mission (11 days) with midodrine (open circles and broken line). Data are modified from Platts et al. [2004].*

Potential limitations and side effects of pharmacological intervention. The primary concern for using pharmacological intervention for space flight countermeasures is timing of drug administration and side effects. In the operational space flight environment, the time that the drug is administered is critical to its effectiveness. For instance, most of the blood pressure raising effect of fludrocortisone results from sodium retention that develops over several days, with the full pressor action being observed in 1 to 2 weeks (Robertson & Davis, 1995). When attempts were made to administer fludrocortisone to astronauts daily over the final 3 to 5 days of the mission, crewmembers complained of painful pressure behind the eyes and discontinued use of the drug [Shi et al., 2004]. This should not be unexpected since headaches in addition to hypokalemia are a common side effect of fludrocortisone (Robertson & Davis, 1995). When applied to astronauts only on the final day of flight, there was no effect on orthostatic responses. Thus, the combination of administration schedule and side effects have rendered fludrocortisone an ineffective countermeasure.

Since plasma concentrations of the most potent metabolite of midodrine peak at 1 hour (Robertson & Davis, 1995), the drug would be most effective operationally if taken before re-entry. With an α_1-adrenoreceptor agonist action, the primary side effect of midodrine is hypertension, particularly in the supine (non-orthostatic) posture. It is therefore likely that the administration of midodrine before re-entry would result in high blood pressure while in orbit.

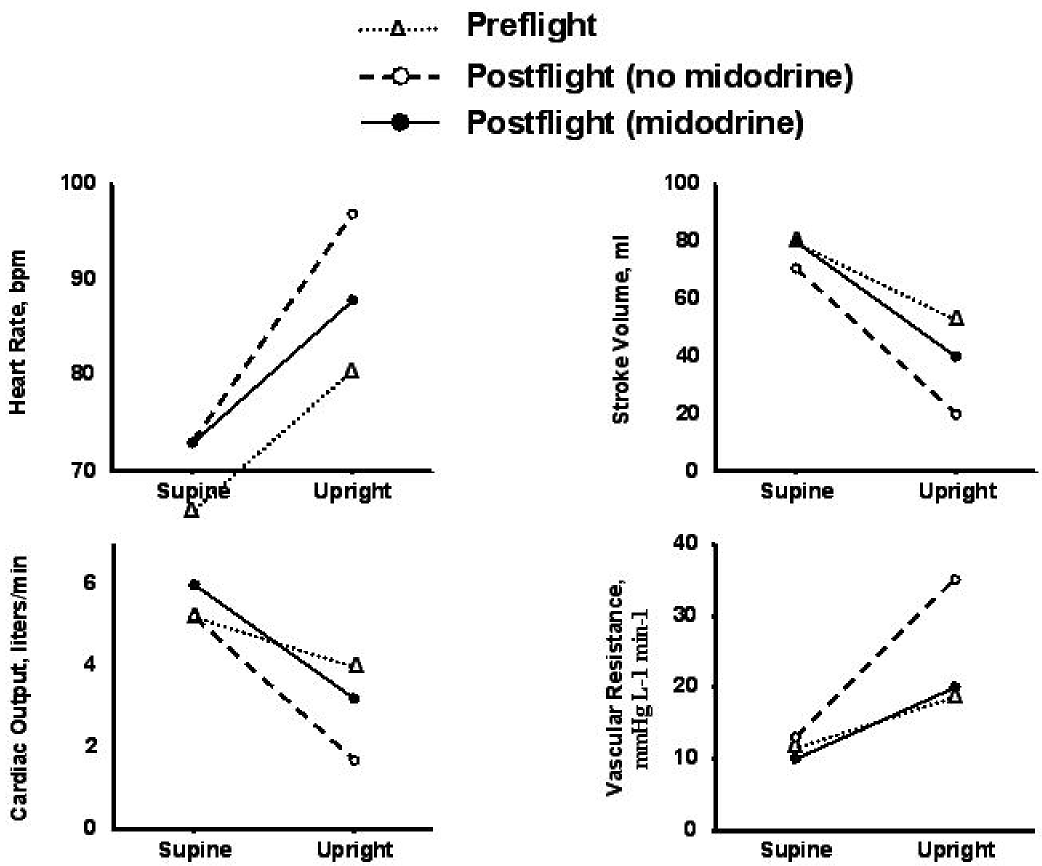

Figure 5. *Heart rate, stroke volume, cardiac output and peripheral vascular resistance responses from supine to upright postures preflight (open triangles and dotted line), postflight without midodrine (open circles and broken line) and postflight with midodrine (solid circles and solid lines). Data are modified from Platts et al. [2004].*

NON-PHARMACOLOGICAL COUNTERMEASURES FOR CARDIOVASCULAR ADAPTATION TO SPACE FLIGHT

Use of a single bout of maximal exercise. The use of physical exercise as a potential countermeasure against post-space flight orthostatic intolerance has been long considered because of the recognized effect of physical activity on circulating blood volume and baroreflex functions. More than a decade ago, specific attention was given to a single exposure of graded exercise designed to elicit maximal effort performed within 24 hours before re-entry from a space mission. In addition to the potential benefits of protecting aerobic capacity (Convertino, 1987), orthostatic tolerance was restored following 16 days exposure to a ground simulation of microgravity when tested 24 hours after a maximal exercise countermeasure was applied (Engelke et al., 1996). Improved physiological functions affected within 24 hours by acute maximal exercise and associated with blood pressure regulation included restoration of blood volume (Convertino et al., 1996), vasoconstrictive reserve (Engelke et al., 1996), and cardiac baroreflex sensitivity (Engelke et al., 1996). Subsequent to ground experiments, a single bout of maximal cycle ergometer exercise was performed by astronauts within 18 to 24 hours prior to landing during space flight missions to test this countermeasure as a possible treatment for post-space flight orthostatic hypotension and intolerance (Moore et al., 2001). Echocardiographic measurements made on the astronauts involved in the testing of the maximal exercise countermeasure demonstrated that stroke volume and cardiac output were restored to pre-flight levels in the exercise group during post-space flight standing, but fell in the control group in a similar fashion as that reported in the ground investigation (Convertino, 2002). Therefore, this exercise regime was successful in targeting the primary mechanisms associated with post-space flight orthostatic intolerance. It is also operationally attractive because it could be performed within 24 hours before the end of a mission and required minimal time of the astronauts (less than 20 minutes only once).

Use of an impendance threshold device (ITD). Recent investigations have focused on the application of a simple concept that central blood volume may be increased acutely by transforming the thorax into a more active vacuum and drawing venous blood from extrathoracic cavities into the heart and lungs. Building on this concept, an inspiratory impedance threshold device (ITD) designed to elevate intrathoracic negative pressure, i.e., create a vacuum, within the chest each time the chest expands

during the inspriatory phase of breathing has been described (Convertino et al., 2005). With the use of an ITD, we have demonstrated in several human experiments that inspiratory resistance can: (a) reset cardiac baroreflex function to a higher operating range for blood pressure (Convertino et al., 2004b); (b) increase stroke volume, cardiac output and arterial blood pressure in normovolemic (Convertino et al., 2004c) and orthostatic (Convertino et al., 2005) subjects; (c) reduce peripheral vascular resistance (i.e., increase vasoconstrictive reserve) (Convertino et al., 2004c); (d) increase cerebral blood flow (Convertino et al., 2005); and (e) reduce orthostatic symptoms (Convertino et al., 2005). Again, the ITD represents a successful approach to targeting the primary mechanisms associated with post-space flight orthostatic intolerance. It is also operationally attractive because it requires little training and easily could be used by an astronaut to avoid cardiovascular collapse associated with post-flight orthostatic instability. Currently the ITD is under consideration for placement in the flight medical bag and on the International Space Station.

	Micro-gravity	Fluid Loading	Florinef	Midodrine	Maxim al Exercise	ITD
Cardiac Baroreflex Function	↓	↔	↔	?	↑	↑
Blood Volume	↓	↔	↑	↑	↑	↑
Stroke Volume	↓	↔	↑	↑	↑	↑
Cardiac Output	↓	↔	↑	↑	↑	↑
Vasoconstrictive Reserve	↓	↔	↑	↑	↑	↑
Orthostatic Response	↓	↔	↑	↑	↑	↑
Aerobic Capacity	↓	↔	?	?	↑	?

Table 1. *Qualitative summary of the effects of microgravity and five pharmacological and non-pharmacological countermeasures on cardiovascular functions associated with risk to astronaut health, safety and performance after a space mission.*

SUMMARY

Impaired cardiovascular responses during standing and performing physical work represent operational risks to astronaut health, safety and performance following space flight. Cardiovascular functions associated with these operational risks include attenuated autonomic baroreflex functions, lower central blood volume, stroke volume and cardiac output, and vasoconstrictive reserve (Table 1). Plasma volume expanders and vasoconstrictors represent the primary pharmacological treatments that have been tested for management of post-flight orthostatic intolerance. Table 1 summarizes the effects of three pharmacological countermeasures in relation to cardiovascular alterations induced by adaptation to microgravity. Saline loading has had little success in reversing adverse cardiovascular adaptations. Fludrocortisone showed promise in ground experiments, but alterations in dose implementation for operational use in space missions showed little positive effects. Midodrine was successful in improving orthostatic tolerance in ground experiments and in one application to space flight. Although pharmacological intervention offers an alternative to treatment of post-flight orthostatic intolerance, there is compelling evidence that intense physical exercise or application of mechanical devices can provide similar physiological effects on acute expansion of baroreflex function(s), central blood volume and vasoconstrictive reserve (Table 1). Since the possibility of side effects or interaction with other drugs exists, the use of pharmacological agents as countermeasures to cardiovascular dysfunctions following space flight should be considered only after the application of more physiologically natural techniques are exhausted.

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